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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/540,658	06/23/2005	Richard A Mathies	UCALP031	5388

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BEYER WEAVER LLP
P.O. BOX 70250
OAKLAND, CA 94612-0250

EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
10/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,658	MATHIES ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-12,14-26 and 37-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-12,14-26 and 37-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 22, 2008 has been entered.

Preliminary Remark

Claims 3, 4, 13, and 27-36 are canceled.

Claims 54-59 are new.

Claims 1, 2, 5-12, 14-26, and 37-59 are pending and are under prosecution.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The new matter rejection of claims 1, 2, 5-12, 14-26, and 37-53 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on February 19, 2008 is withdrawn in view of the arguments presented in the Amendment received on July 22, 2008, specifically pointing to the specification where the purported new matter is supported.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 2, 5-12, 14-26, and 37-53 under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (U.S. Patent No. 5,922,591, issued July 13, 1999) in view of Waller et al. (Applied Environmental Microbiology, 2000, vol. 66, no. 9, pages 4115-4118), made in the Office Action mailed on February 19, 2008 is withdrawn in view of the arguments presented in the Amendment received on July 22, 2008. Specifically, the disclosure of Waller et al. is not drawn to the procedure of immunocapture occurring at a "small" scale so as to be combinable with the microfluidic device of Anderson et al. While the term, "microfluidic" does not necessarily exclude modules of any particular size without an explicit size-exclusion, the rejection is withdrawn based on discovery of an evidentiary reference.

Rejection - New Grounds

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5-12, 14-26, and 37-59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al. (U.S. Patent No. 5,922,591, issued July 13, 1999) in view of Waller et al. (Applied Environmental Microbiology, 2000, vol. 66, no. 9, pages 4115-4118) as evidenced by Hassibi et al. (US 2004/0197845 A1, published October 7, 2004).

Anderson et al. disclose a target detection system, said system comprising:

a) a PCR chamber (column 2, lines 24-27; column 3, lines 33-37; column 9, lines 8-11);

b) a capillary electrophoresis (CE) mechanism (column 15, lines 33-38), and microchannels connecting various chambers (column 2, lines 35-40), wherein the fluid flow is controlled by pneumatically controlled valves (column 4, lines 55-56; column 29, lines 53-54).

With regard to claims 2 and 12, Anderson et al. disclose that their DNA analysis mechanism comprises PCR and CE (discussed above), wherein the artisans explicitly disclose that, "[m]icrocapillary array electrophoresis generally provides a rapid method for size based sequencing, PCR product analysis.." (column 15, lines 46-48).

With regard to claim 5 and 10, the chamber for PCR is disclosed as being used for amplification of DNA obtained from lysing the target of interest (column 6, lines 30-48).

With regard to claims 6 and 14, the capillary is etched microchannel (column 15, lines 63-67).

With regard to claims 7 and 15, the artisans also disclose the necessary step of desalting or purifying the extracted DNA (column 7, lines 17-36).

With regard to claims 23 and 24, the device chamber is formed on a glass layer (column 18, lines 60-63).

With regard to claim 25, the device disclosed by Anderson et al. comprises a plurality of channels (Figure 12C).

With regard to claims 26, 39, 43, 47, and 51, the pneumatic valves are controlled by vacuum (column 29, lines 54-57).

With regard to claims 38, 42, 46, and 50, the target is contemplated as being pathogens (column 6, line 33).

With regard to claims 41, 45, 49, and 53, the artisans employ their valves to direct the fluid directions (see Figure 12C, valves 1262, 1264, 1266, and 1268).

While Anderson et al. explicitly contemplate a microfluidic device which couples both PCR and CE analyses, the artisans are not explicit in stating that their device is adapted for conducting immunocapture (claims 1, 8, 9, 11, 16-22, 37, 40, 44, 48, and 52).

Anderson et al. do not explicitly teach an immunocapture chamber wherein said immunocapture chamber comprises immobilized capture reagents, solid phase capture particles therein, backed bed of beads, magnetically confined beads.

Waller et al. disclose a method of immunocapture PCR assay for the purpose of detecting a pathogenic species, *Campylobacter jejuni* from food samples (see Abstract).

Waller et al. explicitly disclose a step of binding *Campylobacter* in sample by adding polyclonal anti-*Campylobacter jejuni* IgG to the sample, followed by the purification of the antigen-antibody complex with anti-rabbit IgG-coated Dynabeads (page 4116, 1st column, 1st paragraph).

Waller et al. also disclose the step of lysing the captures cells, so as to remove the *C. jejuni* genomic DNA from the antigen-antibody complex, followed by the amplification of said genomic DNA in a PCR reaction (page 4116, 1st column, 2nd and 3rd paragraph).

Waller et al. evidences the well known practice of cleaning up and concentrating the isolated DNA prior to amplification procedure (page 4116, 1st column, 2nd column).

Hassibi et al. disclose a microstructure device (section [0014] and [0230]), wherein immunocapture technique is used to bind and immobilize pathogens of interest using a pathogen-specific or pathogen-selective antibody attached to a magnetic bead or other solid surface, such as the wall of a microfluidic channel in a solid matrix, such as glass, quartz, semiconductor, or plastic chip (see section [0014] and [0042], and [0157]), comprising beads (see Figure 33), followed by the wash and lysis of said pathogens for nucleic acid analysis (section [0015]).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Anderson et al. with the teachings of Waller et al. and Hassibi et al., thereby arriving at the invention as claimed for the following reasons.

Initially, the use of microfluidic device has been well-established in the art, the benefits of which would be certainly recognized by one of ordinary skill in the art, such as being able to conduct series of biological reactions on a single device, resulting in efficiency, reduced chances of contamination, human errors, etc.

Additionally, the use of such microfluidic device for the purpose of detecting various target nucleic acids from a sample, be it for a certain medical condition (i.e., cancer) or for the presence of pathogens from samples, is also well known and recognized in the art of miniaturized biological device.

Whether one of ordinary skill in the art, at the time the invention was made would have been motivated to combine the teachings of Anderson et al. with the teachings of Waller et al. is the question in the present formulation of obviousness. It is respectfully submitted that one of ordinary skill in the art would have been certainly motivated to combine the teachings for the following reasons.

As previously stated, Anderson et al. disclose a microfluidic device, which is capable of amplifying and conducting electrophoresis of the amplified products

However, the amplification method employed by Anderson et al. is drawn to a PCR amplification, which has recognized deficiencies when it comes to the detection of pathogens, one of which is clearly and explicitly identified by Waller et al.:

> "Due to the prevalence of *Campylobacter* species in the food supply, routine and reliable monitoring for these pathogens is necessary in order to reduce their impact upon human health. Cultivation methods involving enrichment, isolation, and biochemical

> characterization require 4 to 5 days to complete…Due to the perishable nature of many food items, a more rapid detection method is necessary to feasibly monitor the potential sources of theses pathogens. For this reason, we have developed an immunocapture PCR method for the detection of *Campylobacter* in foods." (page 4115, 1st column, bottom paragraph)

Hence, one of ordinary skill in the art would have had a clear motivation to fabricate a microfluidic device comprising an assay chamber(s) for conducting immunocapture of pathogens from samples prior to the PCR and capillary electrophoretic analysis, thereby arriving at the invention as claimed.

One of ordinary skill in the art at the time the invention was made would have had a clear expectation of success at combining the immunocapture chamber coupled to the PCR and CE mechanism of Anderson et al., provided the fact that Hassibi et al. explicitly provides that immunocapture module/chamber can be incoporated into a micro-scale device.

The art of microfluidic device has been well-established in the art, which enables an ordinarily skilled artisan to couple a plurality of biochemical reactions, including but not limited to sample purification, enrichment, lysis, amplification, hybridization, etc. (see Zanzucchi et al. patents for example[1]).

Hence, given the motivation provided for by Waller et al. which allows one of ordinary skill in the art to detect pathogens in a sample, wherein the artisans explicitly disclose the uses of antibody and bead assisted immunocapture of pathogens, followed by the lysis of the captured pathogens prior to amplification, one of ordinary skill in the art would have had a reasonable expectation of success at creating a chamber or chambers prior to the PCR-CE detection on the microfluidic device of Anderson et al.

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[1] Zanzucchi et al. holds a plurality of patents which demonstrate feasibility of coupling a plurality of biochemical reactions in a microfluidic device, see for example, USPN 5,585,069 which was filed in November 1994.

Lastly, with regard to providing preconcentration and clean chambers in the device of Anderson et al., it would have been obvious in view of the fact that Waller et al. explicitly disclose the step of cleaning up and concentrating the DNA prior to its amplification. In addition, such practice would have been well within the purview of an ordinarily skilled artisan given the fact that PCR would have been more effective by removing the contaminating cell contents when lysing the pathogens in the sample.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

While Applicants' previous remarks are moot in view of the new ground of rejection, some of the arguments will be addressed to the extent applicable so as to facilitate compact prosecution.

Applicants state that a "**literal** combination of the elements" of Waller and Anderson et al. does not produce a device that might reasonably be expected to function as contemplated by the specification..." (page 11, 4th paragraph, Response).

It is respectfully submitted that the standard of obviousness is not whether or not the teachings of the references are "literally" combinable.

If such standard of obviousness rejection was followed, then most obviousness rejections probably could not be made.

For example, a claim is drawn to a microfluidic device which is tailored for conducting nested-PCR reaction.

If one of ordinary skill in the art were to discover reference A, which teaches a microfluidic device tailored for PCR, with teachings that any variety of known reactions can be tailored in the device, and reference B, which is drawn to a method of nested-PCR in a tube (mL size), wouldn't

that one of ordinary skill in the art be motivated and have a reasonable expectation of success at producing a microfluidic device comprising a module which is tailored to conduct nested-PCR?

For one to say, one of ordinary skill in the art would not be motivated to combine the teachings of the two references because one reference was drawn to a micro-scale, and the other was drawn to macro-scale, and thus, literally non-combinable, would be to dismiss the teachings of reference A which clearly discloses that microfluidic devices are used for allowing many biological reactions to be performed on a single device and the skill and creativity of the ordinarily skilled artisan.

In *KSR International Co v. Teleflex Inc*, the supreme court stated that, "A person of ordinary skill in the art is also a person of *ordinary creativity*, not an automation" (82 USPQ2d at 1397) and that "in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle" and take into account, "the inference and creative steps that a person of ordinary skill in the art would employ" (82 USPQ2d at 1396).

In other words, no one of ordinary skill in the art would think that when making an obviousness rejection, the teachings of the references must be "literally" combinable, but rather employ inference and creativity to fit the teachings together to arrive at the claimed invention.

Applicants next contend that the references do not provide unambiguous motivation to include an immunocapture mechanism on a microfluidic device (page 12, 2nd paragraph, Response).

If Applicants are contending that the references themselves must present motivation for the combination of the references, this issue has been well settled by the courts.

In *in re Oetiker,* 977, F.2d 1443, 1448 (Fed. Cir. 1992), the court stated the following:

> "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and **if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a**

> **prior art reference would lead an inventor to combine the teachings therein with another piece of prior art. This restrictive understanding of the concept of obviousness is clearly wrong**…. While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination…. In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference."

It must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In addition, there was (and currently is) a motivation to combine the teachings of the references. Though not every biological reactions is disclosed in the reference (Anderson et al.), one of ordinary skill in the art would have the skill and knowledge enough to understand that any of the known biological reactions on a microfluidic device can be combined, given the motivation to combine those biological reactions.

This is clearly the case with the instant situation. The motivation to combine immunocapture followed by PCR is explicitly disclosed by Waller et al.

> "Due to the prevalence of *Campylobacter* species in the food supply, routine and reliable monitoring for these pathogens is necessary in order to reduce their impact upon human health. Cultivation methods involving enrichment, isolation, and biochemical characterization require 4 to 5 days to complete…Due to the perishable nature of many food items, a more rapid detection method is necessary to feasibly monitor the potential sources of theses pathogens. For this reason, we have developed an immunocapture PCR method for the detection of *Campylobacter* in foods." (page 4115, 1st column, bottom paragraph, Waller et al.)

Therefore, one of ordinary skill in the art would have had the motivation to conduct immunocapture PCR for pathogenic detection in samples.

Next, turning to whether one of ordinary skill in the art would have been motivated to combine the PCR reaction with CE, Anderson et al. already provides that coupling CE with PCR allows rapid size-based sequencing, PCR product analysis (column 15, lines 46-48; Anderson et al.).

Therefore, one of ordinary skill in the art would have been motivated to combine the immunocapture method with PCR, followed by their analysis with CE.

The only remaining issue is whether or not the one of ordinary skill in the art would have had the skill necessary at the time the invention was made to incorporate an immunocapture module into the microfluidic device of Anderson et al., at a micro-scale (as connoted by the term, "microfliudic").

While it was the position of the Office that such skill was available in the art at the time the application was filed, this issue is further settled by the teachings of Hassibi et al. who explicitly disclose that microfluidic device comprising an immunocapture module was well known in the art at the time invention was filed (already discussed above), having an effective filing date of August 30, 2002.

In *KSR*, the supreme court stated:

> "When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious **unless its actual application is beyond his or her skill**." (page 13, emphasis added).

Clearly, creating an immunocapture module at a micro-scale into a microfluidic device is not beyond the skill of the ordinarily skilled artisan in question, as clearly evidenced by Hassibi et al.

Therefore, it is respectfully submitted that the invention as claimed is deemed *prima facie* obvious over the cited references, for there being a clear motivation to combine the teachings, a clear expectation of success at doing so.

The rejection is maintained therefore.

Double Patenting

The provisional rejection of claims 1-26 and 37 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-39 of copending Application No. 10/750,533 (herein, '533 application), made in the Office Action mailed on July 2, 2007 is withdrawn because the conflicting claims have been canceled in '533 application.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official

Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
10/10/2008

/YJK/